**REMARKS**

The April 2, 2009 Official Action and the references cited therein have been carefully reviewed. In view of the following remarks, favorable reconsideration and allowance of this application are respectfully requested.

At the outset, a shortened statutory response period of three (3) months was set forth in the April 2, 2009 Official Action. Therefore, the initial due date for response is July 2, 2009.

The Examiner has rejected claims 38, 39, 41-47, and 54-56 under 35 U.S.C. §103(a) as allegedly unpatentable over U.S Patent Application Publication No. 2001/0001040 in view of U.S Patent 5,902,610.

Claims 38, 39, 41-47, and 53-56 have also been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as allegedly unpatentable over claims 27-34 of copending U.S. Patent Application No. 10/550,444. Applicants respectfully disagree. At page 5 of the instant Official Action, the Examiner states that "Formula I is defined in the disclosure of Application No. 10/550,444 (figures 26 and 27) to include the instantly claimed compounds, Methyl-TH-DL-Trp, 1-methyl-DL-tryptophan (1MT)." Applicants disagree. Claim 27, from which claims 28-34 of the '444 application depend, recites "with the proviso that formula (I) does not include a compound selected from the group consisting of: 3-(N-methyl-thiohydantoin)-indole", which is methyl-TH-DL-trp (see claim 35 of the instant application. Furthermore, Formula (I) does not encompass 1MT. Accordingly, claims 27-34 of the '444 application do not encompass the species of IDO inhibitors elected in the instant application. In view of the foregoing, the instant double patenting rejection cannot be reasonably maintained. Withdrawal of the rejection is respectfully requested.

Applicants also hereby request that the above provisional double patenting rejection based on claims 27-34 of U.S. Patent Application No. 10/550,444, if maintained, be held in

abeyance until such time as it is the only rejection remaining in the application, whereupon it should be withdrawn so that either the present application or the cited application may be passed to issue, with the provisional double patenting rejection being converted to a non-provisional double patenting rejection in the other application, as authorized by §804 of the MPEP.

The foregoing rejections constitute all of the grounds set forth in the April 2, 2009 Official Action for refusing the present application.

No new matter has been introduced into this application by reason of any of the amendments presented herewith.

In view of the reasons set forth in this response, Applicants respectfully submit that the 35 U.S.C. §103(a) rejection of claims 38, 39, 41-47, and 54-56 and the double patenting rejection of claims 38, 39, 41-47, and 53-56, as set forth in the April 2, 2009 Official Action, cannot be maintained. These grounds of rejection are, therefore, respectfully traversed.

**CLAIMS 38, 39, 41-47, AND 54-56 ARE NOT RENDERED OBVIOUS BY THE '040 APPLICATION IN VIEW OF THE '610 PATENT**

The Examiner has rejected claims 38, 39, 41-47, and 54-56 under 35 U.S.C. §103(a) as allegedly unpatentable over the '040 application in view of the '610 patent. The '040 application allegedly discloses that IDO inhibitors including 1-MT are useful in the treatment of cancer. The '610 patent allegedly teaches that cisplatin is an anticancer that is effectively used against a broad spectrum of cancers. It is the Examiner's position that it would have been obvious to a skilled artisan to combine the above disclosures to arrive at the instantly claimed invention.

Applicants note that claim 53 is not recited in the instant rejection. Accordingly, claim 53 is free of the prior art.

Applicants respectfully disagree with the Examiner's

above conclusion of obviousness regarding claims 38, 39, 41-47, and 54-56. It is a well settled premise of patent law that a proper showing of unexpected results will rebut a prima facie case of obviousness. For example, the MPEP at §716.02(a)(I) states that a "greater than expected result is an evidentiary factor pertinent to the legal conclusion of obviousness ... of the claims at issue." "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with the prior art, can rebut prima facie obviousness" (MPEP at §716.02(a)(II)). "The basic principle behind this rule is straightforward - that which would have been surprising to a person of ordinary skill in a particular art would not have been obvious. The principle applies most often to the less predictable fields, such as chemistry, where minor changes in a product or process may yield substantially different results." *In re Soni* (Fed. Cir., 1995).

At pages 5-6 of the instant Official Action, the Examiner alleges that the instant application has shown "merely additive results" in the combination of cisplatin and 1MT. Applicants strenuously disagree with the Examiner's position.

At the outset, Applicants note that the in the October 15, 2008 Official Action, the Examiner clearly concluded at page 3 that "1MT has no effect when administered alone." As such, it is confusing to Applicants that the Examiner now asserts that the results observed with the combined use of 1MT and cisplatin is "merely additive", particularly when the instant application demonstrates such a dramatic reduction in tumor volume only upon the co-administration of the compounds.

Specifically, the instant application and the supplemental data provided by Applicants clearly show unexpected synergy and results which are significantly greater than "merely additive" with the use of IDO inhibitors such as 1MT and chemotherapeutic agents such as cisplatin. Applicants set forth below 11 examples of unexpectedly superior synergy exhibited by the use of IDO inhibitors such as 1MT and

chemotherapeutic agents such as cisplatin over a wide spectrum of cancers.

First, Figure 5 of the instant application clearly demonstrates a synergistic effect through the co-administration of 1MT and cisplatin in a murine model of autochthonous breast cancer (mmTV-neu mice). Over a two week period, breast tumors in these mice increased in volume approximately three fold without treatment. When 1MT was administered alone, the breast tumors increased in volume approximately two fold over the two week course. Accordingly, the breast tumors still grew significantly in the mice, even with the administration of 1MT. When cisplatin was administered alone, the breast tumors also increased in volume approximately two fold over the two week study, as the tumors had with 1MT therapy. Based on the above, a "merely additive effect" would be about 1-fold change in tumor volume upon the co-administration of 1MT and cisplatin. In stark contrast, Figure 5 of the instant application clearly demonstrates that the co-administration of 1MT and cisplatin resulted in about a 25% ***reduction*** in tumor volume, thereby demonstrating a synergistic effect with the administered compounds. Accordingly, the instant application has clearly demonstrated that the instantly claimed methods yield results which are vastly superior compared to "merely additive results", as alleged by the Examiner. Indeed, a skilled artisan would not anticipate that combining two agents which merely slow tumor growth would result in the reduction of tumor size. The reduction in tumor size indicates that tumor cells have been killed (e.g., by the induction of apoptosis), whereas the mere slowing in the increase of tumor volume only demonstrates an inhibition of tumor growth.

Second, Figure 4A of Muller et al. (Nature Medicine (2005) 11:312-319; submitted previously) demonstrates similar results. Indeed, Muller et al. used the same murine model of autochthonous breast cancer (mmTV-neu mice). As with the instant application, Muller et al. demonstrate that untreated

breast tumors increase in size 3.0-fold after two weeks. When 1MT was administered, breast tumor growth was slightly retarded and the tumor grew 1.8-fold. The administration of paclitaxel had almost no effect as breast tumors grew 2.4-fold. Accordingly, an additive effect from the combined use of the compounds would be about a 1.2-fold ***increase*** in tumor volume. In complete contrast, Figure 4A of Muller et al. demonstrates that the tumor ***decreased*** 30% in size (0.7 fold). Again a significantly greater than additive effect has been demonstrated with the administration of 1MT and a chemotherapeutic agent.

Third, Figure 6A of Muller et al. also demonstrates a synergistic effect with the co-administration of methyl-TH-Trp and the chemotherapeutic agent paclitaxel. Again, without treatment, the breast tumors in the murine model increased in volume 3-fold and the administration of paclitaxel had little effect as breast tumors till grew 2.4-fold. When methyl-TH-Trp was administered, breast tumor growth was slightly retarded and the tumor grew 1.8-fold. In view of the foregoing, an additive effect from the combined use of the compounds would yield about a 1.2-fold ***increase*** in tumor volume. In stark contrast, Figure 6A of Muller et al. demonstrates that the tumor ***decreased*** 45% in size (0.56 fold) with the co-administration of methyl-TH-Trp and the chemotherapeutic agent paclitaxel. Therefore, unexpected synergy has been demonstrated.

Fourth, Exhibit B provided with the Declaration by George Prendergast submitted with the July 7, 2008 Official Action response also demonstrates greater than "merely additive results." The data presented in Exhibit B shows the effect of cyclophosphamide and/or 1MT on a murine colon cancer. After 22 days, tumor volume increased to approximately 250 $mm^3$. The administration of 1MT alone yielded no effect. In other words, the tumor grew as much without treatment as with 1MT. When cyclophosphamide was administered, tumor growth was retarded to approximately 110 $mm^3$. As such, the additive

effect of the two compounds would also yield a tumor of approximately 110 $mm^3$, as 1MT had no effect. In contrast, Exhibit B demonstrates that tumor volume was reduced to approximately 75 $mm^3$, thereby demonstrating unexpectedly superior results and synergy.

Fifth, Exhibit A provided with the Declaration by George Prendergast submitted with the July 7, 2008 Official Action response also demonstrates greater than "merely additive results" in a lung cancer model. After 22 days, an untreated lung tumor had a volume of approximately 240 $mm^3$. With the administration of 1MT, tumor volume was slightly reduced to about 190 $mm^3$ after 22 days. The administration of cyclophosphamide reduced the tumor volume even more to approximately 130 $mm^3$. Based on the above, the combined effect of the two compounds would be expected to reduce tumor volume to about 80 $mm^3$, if one assumed an additive effect (240 - (240-190)-(240-130) = 80). Again, in contrast to these additive results, Exhibit A demonstrates that the co-administration of an IDO inhibitor such as 1MT with a chemotherapeutic inhibitor such as cyclophosphamide results in synergy and unexpectedly superior results, as the tumor volume was reduced to about 30 $mm^3$, well below the 80 $mm^3$ additive result.

Sixth, Figure 1A of Hou et al. (Cancer Res. (2007) 67:792-801; submitted previously) also demonstrates synergistic effects in a melanoma model. After 28 days, the untreated melanoma tumor area was approximately 290 $mm^2$. The tumor area after the administration of cyclophosphamide was also about 290 $mm^2$. Notably, tumor area ***increased*** to about 330 $mm^2$ with the administration of 1MT. Therefore, the additive effect of these compounds should lead to a tumor area of about 330 $mm^2$. In stark contrast to these additive effects, Figure 1A demonstrates strong synergy between 1MT and the chemotherapeutic agent cyclophosphamide as the tumor area was reduced to about 130 $mm^2$.

Seventh, Figure 1C Hou et al. also demonstrates a synergistic effect when the chemotherapeutic agent was

replaced with irradiation. Indeed, in the absence of any treatment, tumors were approximately 310 $mm^2$ after 21 days. The administration of irradiation alone or 1MT alone yielded tumors of approximately 275 $mm^2$. An additive effect for the two treatments would yield a tumor having a area of about 240 $mm^2$. In contrast, Figure 1C shows that the combined therapy yielded a tumor area of ~160 $mm^3$ after 21 days. As such, synergy was again demonstrated.

Eighth, Figure 5A of Hou et al. also demonstrates that the stereoisomer D-1MT exhibits synergistic effects with the administration of a chemotherapeutic agent. Without treatment, the tumor area is shown to be about 300 $mm^2$ at 24 days. The administration D-1MT actually ***increased*** the tumor area to about 320 $mm^2$. The administration of cyclophosphamide alone yielded a tumor area of about 200 $mm^2$. Accordingly, an additive effect would yield a tumor of ~220 $mm^2$. As seen in Figure 5C, the administration of D-1MT with cyclophosphamide yielded a tumor area of only 110 $mm^2$, significantly lower than the "mere additive" result.

Ninth, Figure 5B demonstrates that the synergistic effect is observed when the chemotherapeutic agent is gemcytabine. With no treatment, the melanoma tumor had a tumor area of ~310 $mm^2$. The administration of D-1MT alone again ***increased*** tumor area compared to controls to about 320 $mm^2$. Gemcytabine therapy also yielded little to no effect as the tumor area was approximately 300 $mm^2$. Combining these results yield an anticipated tumor area of 310 $mm^2$, when using an additive approach. As seen in Figure 5B, tumor area was reduced to ~180 $mm^2$, thereby demonstrating significantly greater results than the above additive effect.

Tenth, Figure 2B of Kumar et al. (J. Med. Chem. (2008) 51:1706-1718; submitted previously) also demonstrates a synergistic effect between the IDO inhibitor vitamin K3 and the chemotherapeutic agent paclitaxel. Figure 2B demonstrates that the untreated breast tumors increased in size 2 fold over a 2 week period. The administration of paclitaxel alone

showed a slight retardation in tumor growth as the tumor volume increased 1.7 fold. The administration of vitamin K3 alone also showed a slight inhibition of tumor growth with as the tumor volume increase 1.4 fold. Combining these results, one would expect a tumor volume ***increase*** of 1.1 fold when the agents were administered together. In stark contrast, Figure 2B demonstrates that tumor volume ***decreased*** significantly when the IDO inhibitor and chemotherapeutic agent were combined (0.39 fold change; i.e., a 60% decrease in tumor volume), thereby demonstrating synergy.

Lastly, the Examiner states at page 5 of the instant Official Action that the results presented in Example 4 of the instant application are "merely additive." Applicants respectfully disagree. As seen in Example 4, Table 1, and Figure 11, untreated mice exhibited a ~200% increase in breast tumor volume. The administration of 1MT alone or cisplatin alone yielded a slowing in tumor growth to about 50% of the untreated tumors. In contrast, the combined administration of 1MT and cisplatin unexpectedly caused the tumor to reduce in size by almost 30%. Furthermore, the combined administration resulted in "pronounced hemorrhage, apoptosis, and infiltration of CD3-positive T cells." These histological and immunohistochemical changes were **NOT** observed with either agent alone. Accordingly, the instant application has demonstrated clearly synergistic effects and unexpected results (e.g., apoptosis only with the co-administration of the two compounds) through the co-administration of 1MT and cisplatin.

In view of the foregoing, it is clear that the administration of an IDO inhibitor with a chemotherapeutic agent leads to synergistic effects and greater than "merely additive" results across physiologically and etiologically distinct cancer species encompassed by the genus cancer and with a wide variety of IDO inhibitors and a wide variety of chemotherapy (e.g., chemotherapeutic agents and irradiation). As such, a skilled artisan would expect these synergistic

effects to be present among all cancers.

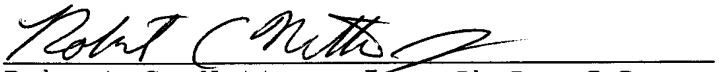
In view of the foregoing, Applicants respectfully submit that the rejection of claims 38, 39, 41-47, and 54-56 under 35 U.S.C. §103(a) is untenable and should be withdrawn.

**CONCLUSION**

In view of the amendments presented herewith and the foregoing remarks, it is respectfully urged that the rejections set forth in the April 2, 2009 Official Action be withdrawn and that this application be passed to issue.

In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to call the undersigned at the phone number given below.

Respectfully submitted,
DANN, DORFMAN, HERRELL AND SKILLMAN
A Professional Corporation

By 
Robert C. Netter, Jr., Ph.D., J.D.
PTO Registration No. 56,422

Telephone: (215) 563-4100
Facsimile: (215) 563-4044